

# **RISK OF BREAST CANCER BY INDIVIDUAL INSULIN USE - AN INTERNATIONAL MULTICENTER STUDY**

**Running title** Breast cancer and individual insulins

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## **Abstract**

**OBJECTIVE** Several studies have been published in 2009 suggesting a possible association between insulin glargine and increased risk of malignancies, including breast cancer. The objective of this study was to assess the relation between the individual insulins (glargine, aspart, lispro and human insulin) and development of breast cancer.

**RESEARCH DESIGN AND METHODS** 775 incident cases of primary invasive or *in situ* carcinoma breast cancer occurring in women with diabetes from 92 centers in the U.K., Canada and France were matched to a mean of 3.9 diabetic community controls (n=3050; recruited from 580 general practices) by country, age, recruitment date, diabetes type and management. The main risk model was a multivariate conditional logistic regression model with case/control status as the dependent variable and individual insulin use, 8 years preceding the index date, as the independent variable, controlling for past use of any insulin, oral anti-diabetic drugs, reproductive factors, lifestyle, education, hormone replacement therapy and history of contraceptive use, BMI, comorbidities, diabetes duration, and annual number of physician visits. Glargine was also compared to every other insulin by computing all ratios using the variance-covariance matrix of logistic model parameters.

**RESULTS** Adjusted odds ratios of breast cancer for each type of insulin vs. no use of that insulin were: 1.04 [95% CI 0.76-1.44] for glargine; 1.23 [0.79-1.92] for lispro; 0.95 [0.64-1.40] for aspart; and 0.81 [0.55-1.20] for human insulin. Two-by-two comparisons found no difference between glargine and the different types of insulins. Insulin dosage or duration of use and tumor stage did not change the results.

**CONCLUSIONS** This international study found no difference in the risk of developing breast cancer in patients with diabetes among the different types of insulin with short- to mid-term duration of use. Longer term studies would be of interest.

Several studies have suggested an association between the risk of malignancies and the therapeutic use of insulin (1,2). Insulin therapies include human insulin, analogs of human insulin, and animal insulin. Following the simultaneous publication of three studies comparing different insulin preparations for associated cancer risk, it was suggested that users of glargine, a long-acting insulin analogue, had an increased risk of cancer and particularly of breast cancer (3–5). As a result, the European Medicines Agency (EMA) and the United-States Food and Drug Administration (FDA) issued an alert in July 2009 informing healthcare professionals and patients about a possible increase of cancer incidence in glargine users (6,7). These studies had important methodological limitations, including lack of proper control for breast cancer risk factors,(8,9) and their results were not subsequently confirmed (10).

The objective of this international case-control study was to assess the relation between use of individual types of insulin (glargine, aspart, lispro and human insulin) and development of breast cancer, controlling for breast cancer risk factors, type, severity and history of diabetes, and comorbidities (11).

## **RESEARCH DESIGN AND METHODS**

### **Study population**

In this case-control study, breast cancer cases and community controls were women aged 18 years and over, who had been treated for type 1 or type 2 diabetes with any type of anti-diabetic drugs (oral and insulin) for at least three months, were alive and able to answer a telephone interview and living in the United Kingdom (England and Scotland), Canada (Quebec, Ontario and New-Brunswick) or France (nationwide). Women previously treated for gestational diabetes for less than 3 months or suffering from psychiatric or other medical conditions preventing participation were excluded. Recruitment took place between January 2010 and June 2012.

### *Cases*

Cases of breast cancer were identified in oncology clinics that treated more than 100 breast cancer patients annually in each participating country/region. Pathology records were searched to identify women meeting the aforementioned inclusion and exclusion criteria and who had a first lifetime pathologically-confirmed diagnosis of breast cancer between January 1, 2008 and June 30, 2009, which corresponds to the eighteen-month period prior to the international alert issued on glargine. All hospital charts were reviewed, and patients whose records suggested a history of diabetes (type 1 or type 2) were invited to participate in the study. Information was collected from computerized oncology records on the type of breast cancer (*in situ*, ductal or lobular, primary invasive), TNM classification, examinations and treatments. Based on TNM, cancer was secondarily staged from 0 to 4 according to the American Joint Committee on Cancer (AJCC version 7) classification. Types of breast cancer tumors were also classified as HER2 positive, luminal or triple negative.

### *Controls*

Controls were identified through a pool of referents recruited by networks of GPs participating in the Pharmacoepidemiologic General Research eXtension (PGRx) program. This research network systematically recruits representative patients from general practice using a methodology that has been previously validated in risk-assessment studies (12). In this particular instance the PGRx recruitment system consisted, in each participating country and region, of a random sample of participating GPs instructed to identify and invite all their patients diagnosed with diabetes before June 30, 2009 (and meeting all of the inclusion and exclusion criteria mentioned above) to participate in the study.

### **Data collection**

History of diabetes, risk factors and prescriptions were obtained from each participant's own diabetologist and/or GP involved in the treatment of their diabetes (cases and controls).

Detailed data on diabetes (type, age at diagnosis, duration, history of anti-diabetic treatments), complications (renal, vascular, ophthalmological and neurological), and current and past HbA1c results, were collected for cases and controls. All available HbA1c results were computed for each participant, allowing classification of patients according to a 3-class variable [mode level:  $\leq 6.5\%$  ( $\leq 48$  mmol/mol), 6.6-8% (49-64 mmol/mol),  $> 8\%$  ( $> 64$  mmol/mol)].

All cases and controls underwent an identical telephone interview especially developed for the PGRx research program using a proprietary methodology called progressive-assisted backward-active recall (PABAR) previously validated (13,14). Patients were sent an interview guide ahead of time including a review of medications commonly used, listed by health problem category (cardiovascular, respiratory, metabolic, etc.). Patients were asked to provide as many prescriptions as possible. Following reporting of anti-diabetic drug use, patients were prompted to review the list of all anti-diabetic drugs and types of insulin available on the market (trade and generic names) assisted by trained interviewers blind to the specific breast cancer hypothesis of the project. The interview also collected information on education and socioeconomic status, smoking, alcohol consumption and physical activity, personal and first-degree relatives' history of breast, ovarian and any other cancer, and a review of past and present medical history with a focus on diabetes-related comorbidities including retinopathy, arteriopathy, nephropathy and peripheral neuropathy. Interview also included lifetime reproductive and hormonal history including age at menarche, menopausal status and age at menopause, parity and age at first and last birth, breastfeeding, use of oral contraceptive and hormonal replacement therapy (HRT). Body mass index (BMI) corresponding to the current, highest and lowest weights between 2001 and 2008 was computed and classified in three categories:  $< 25$ , 25-29 and  $\geq 30$  kilograms per height in meters squared ( $\text{kg/m}^2$ ).

## Exposure to insulin

Objective prescribing information on insulin from physicians and/or pharmacists was obtained in 84.4% of patients (i.e., information provided by physicians and/or pharmacists). In the remaining patients, data on insulin exposure was obtained from the patient interview only (see below). Agreement between patient interviews and physicians' records for insulin use was 97% ( $\kappa > 0.89$ ) in patients where information from both sources was available. Given that all patients underwent an interview, the primary analysis used the data collected during the interview while objective data from prescriptions was used in sensitivity analyses. The time-window retained *a priori* for the primary analysis was insulin use in the 8-year period preceding the index date defined as the date of first diagnostic biopsy confirming breast cancer for the case. An identical time window was used for the controls so as to match controls to each case (see matching rules below). This time-window corresponded to the time elapsed between the date back when glargine was first marketed (Fall 2001) and the last possible index date accepted for the study (June 30, 2009). Cases and controls were individually classified as exposed or non-exposed to each insulin type within this time-window. Diabetes treatment included all types of insulin, metformin and other oral anti-diabetic drugs. Insulin use was classified as basal or prandial, but also by type of molecule (human insulin, aspart, glargine, lispro, and other types such as detemir, glulisine and animal). Detailed history for each category of treatment before the index date was collected: start/stop dates, doses, and switching. The total duration of each insulin use period was computed. Patients who reported to have used insulin for less than 3 months (total treatment duration) were classified as non-exposed to insulin. Doses were classified as either lower or higher than the median value for each individual insulin use in controls. Use of any insulin prior to the 8-year time window of interest was defined as "past-insulin use" without distinction between individual types of insulin.

## **Statistical analysis**

The statistical analysis plan was finalized before the start of data collection.

Participants were compared to non-participants for age, cancer stage (for cases), and anti-diabetic treatments (oral therapy and insulin use). Given that some patients were dead by the time the study began, death rates according to the type of anti-diabetic treatment (oral, glargine and other individual insulins) reported in the records were computed in order to detect a potential survival bias.

### *Matching*

Once all cases and potential controls were interviewed, controls were randomly matched to cases on five criteria: type of diabetes (type 1 or 2), country region or province, age at recruitment ( $\pm 1$  year if possible, otherwise  $\pm 2, 3, 4$  or 5 years), date of recruitment ( $\pm 6$  months) and referral to an endocrinologist (diabetologist) for diabetes (Yes/No). The objective was to obtain on average four matched controls per breast cancer case.

### *Modeling diabetes risk factors and insulin exposure*

A multivariate confounding breast cancer risk score was computed to be used as adjustment variable using socio-demographic, lifestyle (smoking, alcohol consumption and physical activity) and reproductive factors (age at menarche, parity, breastfeeding, menopause, use of oral contraceptives and hormonal replacement therapy), body mass index, personal history of cancer and history of breast cancer in first-degree relatives. Individual variables associated to the case/control status were used to control for residual confounding. Unadjusted and adjusted matched odds ratios (ORs) and their 95% CI were computed using conditional logistic regression with the case/control status as the dependent variable. Individual insulin use of glargine (Yes/No), lispro (Yes/No), aspart (Yes/No), human insulin (Yes/No), other types of insulin (Yes/No) within the 8 years preceding the index date and past use of insulin (Yes/No) were all entered in the models, thus allowing for mutual adjustment. In the adjusted models,



OR estimates were controlled for multivariate confounding breast cancer risk score (in quartiles), BMI ( $\leq 24$ , 25-29,  $\geq 30$  kg/m<sup>2</sup>), duration of diabetes ( $< 10$  years,  $\geq 10$  years), number of annual visits to a physician before the index date, cardiovascular disorder or other medication use (at least one), presence of comorbidities ( $< 3$ ,  $\geq 3$ ), past use of insulin (Yes/No), and any use of oral anti-diabetic drugs (Yes/No). ORs corresponding to each insulin product allowed for comparison between users and non-users of each type of insulin individually, both categories containing users and non-users of other insulins. These ORs were mutually adjusted and reflect the association of breast cancer with the insulin product considered adjusted for the use of other insulins. Sensitivity analyses were performed in users of at least one insulin treatment in the past and in users of at least one insulin treatment in the 8-year time window. Looking specifically at glargine, a stratified analysis by duration of glargine use ( $< 4$  years and  $\geq 4$  years) and by maximum dose used (below or above median dose in the study population, i.e. 27 UI) was performed. Additionally, breast cancer risk estimates associated with glargine were compared to every other insulin by computing all ratios using the variance-covariance matrix of logistic model parameters.

No variable used in the analyses had more than 5% of missing values. In all multivariate models, missing values were imputed by median (if continuous) or mode (if categorical). The study was powered to detect an odds ratio as small as 1.4 for glargine use and breast cancer. Recruitment was stratified by country (U.K., France and Canada) to account for variations in glargine use and ensure sufficient exposure. Analyses were performed using the SAS® software (version 9.1.3; SAS Institute Inc., Cary, North Carolina, USA).

## **Ethics**

The study protocol, consent forms and methods for protecting the confidentiality of patients were approved by institutional review boards across the three participating countries.

Research ethics committees' approval was obtained for each participating institution and for recruitment by GPs in the U.K. and Canada. In France, ethics approval was obtained from the *Commission nationale de l'informatique et des libertés* (CNIL) and from the *Conseil national de l'ordre des médecins* (CNOM). Written informed consent was obtained from each participating patient. Physicians received fixed fees for their participation but not patients.

## RESULTS

### Description of cases and controls

Overall, 92 participating oncology centers (39 in the U.K., 38 in France, and 15 in Canada) reviewed a total of 39 558 medical records of women with a pathologically confirmed first lifetime diagnosis of breast cancer made between January 1, 2008 and June 30, 2009 (Figure 1). Among them, 3 131 (7.9%) breast cancer patients were found to have a record of diabetes in the chart, of which 396 (12.6%) were dead at the time of study. Death rates were higher in insulin users than in non-users, but were comparable between users of any insulin (18%) and users of glargine (17%). Thus, 2 735 (87.4%) patients were available to participate in the study. Among the latter, contact details were available for 2 408 (88.0%) patients, therefore allowing to seek consent to participate in the study; all patients were contacted and 997 (41.4%) accepted to participate. Nonparticipating cases had a similar age as participants [mean age 67.0 (SD: 11.7) and 66.8 (9.1) years, respectively] and similar use of any type of insulin as registered in the oncology center record [16.2% vs. 14.5% (any prandial insulin) to 17.8% (any basal insulin), respectively]. Participating cases were primary invasive cancers in 89% of instances and cancers *in situ* in the remaining 11%. According to the AJCC classification, 58.1% of patients were stage 0-1, 30.4% stage 2, and 11.5% stage 3-4. Data on hormone receptors (available in 652 cases) showed that 76.5% of cancers were estrogen- and/or progesterone-receptor positive and HER2 negative (luminal). Subsequently, 88 (8.8%) patients could not be reached for the interview. Out of 909 interviewed cases, 797 cases were

eligible for matching with controls after secondary exclusion due to exclusion criteria found during the interview.

For controls, 580 GPs across the three countries recruited 5329 patients with diabetes agreeing to participate in the study (Figure 2) which was estimated (using respective national statistics) to represent between 44% and 52% of the expected clientele with diabetes seen in general practices, a participation rate similar to that of cases. Subsequently, 769 patients (14.4%) were identified as not meeting the inclusion and exclusion criteria and further 890 (16.7%) could not be reached for the interview, leaving 3670 control patients available for matching to each case.

After the matching procedure, 22 cases and 620 controls could not be matched leaving a final study population of 775 breast cancer cases (21% from the U.K., 15.5% from Canada, and 63.5% from France) and 3050 controls for a mean of 3.9 controls per case (range: 1-10).

Cases and controls did not show major differences for variables concerning lifestyle, medications use and utilization of healthcare services (Table 1). As expected, cases had more often a personal and family history of breast cancer (odds ratio [OR] 1.53 [95% CI 1.16-2.02] and 1.65 [1.34-2.01], respectively). They were also more often after menopause (2.65 [1.70-4.14]) and reporting current or past use of hormone replacement therapy (1.38 [1.10-1.73]).

The probability of a case to fall within the fourth quartile of the computed breast cancer risk score was much higher than controls (2.74 [2.05-3.68]). Table 2 presents the main features of diabetes history and management which were very similar between cases and controls for all the variables studied. The distribution of the two types of diabetes by matching was identical in cases and controls with 6.2% for type 1 diabetes. Use of any insulin (cases and controls combined) was independently and significantly associated with longer duration of diabetes, HbA1c >8% (>64 mmol/mol), cardiovascular comorbidities as well as recent hospitalization ( $\leq 1$  year) (data not shown). No significant association with insulin use was found for current

BMI, age, education or multivariate confounding breast cancer risk score. Patients with type 1 diabetes were more likely to use glargine than any other type of insulin; no other variable was associated to glargine use, comparatively to other insulins (data not shown).

### **Individual Insulin and risk of breast cancer**

None of the individual insulins was associated with an increased risk of breast cancer (Table 3). Comparisons between types of insulin use showed no significant differences in the risk of breast cancer, with odds ratio 0.85 [0.48-1.50] for glargine vs. lispro, 1.10 [0.64-1.89] for glargine vs. aspart and 1.29 [0.78-2.13] for glargine vs. human insulin. No statistical difference was observed in the proportion of glargine users according to the AJCC staging for breast cancer (stage 0: 10.8% of users, stage 1: 8.5%, stage 2: 12.3%, stage 3 or 4: 9.0%) or the tumor type (luminal: 9.0%, HER2 positive: 8.1%, triple negative: 14.8%). Results were similar when medical information from prescriptions, rather than patient interviews, was used as the source of information on exposure. Sensitivity analyses of patients with uncertain exposure did not change the results.

The mean duration of glargine use in the whole study population (cases and controls) was 3.2 years (SD: 2.0). The adjusted OR for risk of breast cancer did not change with increasing duration of glargine use, with 1.15 [0.70-1.88] for less than 4 years and 0.94 [0.51-1.74] for 4-7 years. Finally, in analyses restricted to insulin users, we observed that categorizing of glargine use in high and low dose returned no trend whatsoever (no use above 27 IU: 1.10 [0.61-1.97]; at least one use above 27 IU: 1.02 [0.59-1.75]) (Table 3).

### **CONCLUSIONS**

This international case-control study was specifically designed to address the question of breast cancer risk among patients with diabetes using different insulin regimens and was carefully designed to minimize the risk of biases common to this type of studies. The no-difference findings in breast cancer risk in users of any of the individually studied insulin

(glargine, aspart, lispro, and human insulin) were all fully consistent in the various sensitivity analyses. Further analyses focusing on insulin glargine found no evidence to suggest that either dose or duration of glargine use influenced the risk of breast cancer. This study did not adequately explore the hypothesis that insulin could promote cancer foci development and could not address the effect of long-term exposure since insulin analogs (glargine, lispro, aspart) have been marketed only from 2001 onward. More recently marketed (detemir) or very infrequently used insulin types (glulisine, porcine) could not be included in this study. Most previous studies on individual insulin use and breast cancer have been conducted by record-linkage of healthcare databases (3–5). The first study to suggest a potential risk of glargine vs. human insulin, found an OR of 1.31 [1.20-1.42] for breast cancer in high-dose users only (>50 UI), while only controlling for a limited number of factors (3). A study from the Scottish Diabetes Research Network in different subgroups of patients (5) reported hazard ratios for glargine and breast cancer varying from 1.49 [0.79-2.83] to 3.39 [1.46-7.85] but information on dose and other important risk factors was lacking: the authors concluded that confounding by indication was likely to have occurred as patients receiving glargine were older and exhibited higher severity of diabetes. After a preliminary study estimating the relative risk for glargine and breast cancer to be 1.99 [1.31-3.03], another Swedish group performed two subsequent cohort follow-ups and found a relative risk of 0.87 [0.41-1.85] for glargine and breast cancer in their most recent analysis (4,15). Differences in results were attributed to random fluctuation. A study based on U.K. General Practice Research Database (GPRD) did not find any association between risk of breast cancer and glargine use (10), whereas another study on the same database showed that the risk of breast cancer tended to increase after 5 years of glargine use (1.8 [0.8-4.0]), and significantly so for the women who had been on insulin before starting glargine (2.7 [1.1-6.5]), indicating a possible cumulative effect (16). A retrospective nested case-control analysis in an Italian cohort of new insulin

users found an elevated OR for glargine use and breast cancer (5.43 [2.18-13.53]) (17); this study lacked controlled matching for diabetes management, undoubtedly a potentially major confounder for case-control research in pharmacoepidemiology. Finally, analyses of the French national healthcare insurance database found no excess of cancer ([HR] 0.59 [95% CI 0.28-1.25]) or cancer deaths (0.58 [0.32-1.06]) among exclusive users of glargine compared to human insulin (18). The large mortality deficit between the two populations might reflect a lack of comparability between populations.

A common issue inherent to studies conducted by record linkage of healthcare databases is that it usually allows access to a limited number of risk factors for the control of confounding. In our study, however, a large number of risk factors were considered and carefully evaluated. Unexpectedly, the analysis showed no impact from the inclusion of these factors into risk models on odds ratio estimates: crude and adjusted odds ratios were similar.

### **Interpretation**

Exposure to insulin was thoroughly documented within the eight-year time window (2001 to 2009), therefore spanning all potential exposures to glargine and other insulin analogs before the alert on insulin glargine and breast cancer was issued. Documenting past insulin use before that time window (obtained through patient interviews) allowed controlling for potential cumulative insulin effects. Still, the eight-year time window remains a relatively short period for cancer latency, but it might be sufficient to cover any potential effect on tumor growth. Moreover, very few patients had been continuously exposed to one specific type of insulin during the whole eight-year period. Among glargine users, only one-third had been exposed to that insulin during four years or more. For other insulins, exposure durations lasted for less than four years in the majority of users. Human insulin is a growth factor for different tumors *in vitro* and elevated levels of circulating endogenous insulin produce a secondary increase of insulin growth factor-1 (IGF-1) *in vivo*. This has been shown to

accelerate the progression of cancer foci (19-22). Glargine's affinity for the IGF-1 receptor is very high, which justifies concerns about its potential ability to promote cancer growth.

However, it was shown recently that glargine itself is rapidly metabolized and that its metabolites have lower affinity for IGF-1 than endogenous insulin (23). In our study, the prevalence of glargine use was similar for all tumor stages (0 to 4) and types (luminal, HER2 positive or triple negative) studied, which was reassuring in this respect.

### **Strengths and limitations**

The main strength of this study was the comprehensive procedure by which drug exposure and information on individual risk factors (24) were collected, using a methodology that has been previously used and validated (12,13). Data was collected from clinical practice, which allowed thorough documentation of patients' history of diabetes, including severity, comorbidities and management by either diabetologists or general practitioners. It accurately documented the prevalence of known risk factors for breast cancer allowing their adjustment in the analyses. Crossing data from physicians' records and standardized patient interviews allowed to establish the lifetime history of insulin treatment, documenting the time between first diagnosis of diabetes and first insulin therapy, as well as different individual insulin regimens used during and prior to the time window of interest for this study.

The case-control design of this study is the best suited to test hypotheses on risk of relatively rare events but has several limitations. First, selection bias can occur when identification of cases is associated with exposure status. The large number of breast cancers screened (39 558) to identify patients exposed to anti-diabetic drugs, by trained research assistants independently from the investigators, reduced this possibility. Nevertheless, based on data from oncology records, the participation of patients was not independent of exposure. Overall, 51% of patients declaring themselves as glargine users agreed to participate in the study compared to 41% for users of any other type of insulin. This difference was due to cases from

the U.K. (participation rates: 56% in glargine users vs. 37% in users of other insulins,  $p > 0.05$ ), while no difference was found in Canada and France. Participation was identical in oral anti-diabetic users and non-users (40%), and did not differ across the three countries. Chance or subtle encouragement of glargine users to take part in the study might explain this. Yet, in this case, a bias would act against our findings (null hypothesis). Excluding data from the U.K. in sensitivity analysis did not change the results ([OR] 1.04 [0.72-1.50]).

Case-control studies are mostly at risk of recall bias where the exposure of interest is more likely to be reported by patients experiencing the condition of interest (i.e., cancer).

Precautions to prevent this bias included collecting medical prescriptions and records from health professionals and crossing the latter information with interviews, which gave excellent agreement for insulin use (97%). Sensitivity analyses using one or the other source of information did not change the results. Also, a potential recall bias would work in favor of an association between glargine and breast cancer. Another bias could arise from a diagnosis (of cancer) that is not blinded to exposure status. This is why this study was conducted only in cases diagnosed before the issued alert. The fact that the prevalence of glargine use was similar across the different stages of cancer is also reassuring in this respect as “lead-time bias” (when early diagnosis falsely appears to prolong survival) is thus less likely.

A disadvantage of the case-control approach is that only patients alive at the time of the interview could be included. A survival effect was unlikely to bias the comparison between different types of insulin because the death rate in cancer cases at the time of recruitment in the study was the same in glargine users (17%) as opposed to other insulin users (18%).

Another important potential limitation may be attributed to the relatively low participation rate. Our study was powered *a priori* to detect an odds ratio of at least 1.4 for glargine use relative to non-use of insulin based on the recruitment of 750 cases and 3000 controls. This required screening nearly 40 000 incident breast cancers, which is equivalent to the number of



annual incident breast cancers registered in countries such as the U.K. or France. Clinical characteristics of participating breast cancer cases were consistent with breast cancer statistics for age, type of cancer, stage, and hormonal receptor distributions;(25–28) the type and severity of diabetes, as well as the prevalence of insulin use (including by individual types) were also representative of patients with this disease in current practice, providing reasonable evidence of representativeness of the study population. Computation of breast cancer risk for factors such as reproductive history, HRT and oral contraceptives, was consistent with previously reported data. We did not observe, however, a risk with obesity, which has been frequently associated with a higher risk of breast cancer (29). This may be explained by the fact that the majority of our patients (cases and controls) were overweight or obese. Finally, this case-control study assessed only one cancer site (breast cancer). Recent studies on individual insulin use and cancer have provided additional information on other cancers. The continuation of the ORIGIN trial over 6 years found no evidence of increased risk for any type of cancer (30). The same was true for a number of recent healthcare database studies (31,32).

In conclusion, this international case-control study specifically conducted to address the risk of individual insulin use and incident breast cancer after a mean exposure of 3.2 years, found no increased risk with none of the individual insulin studied (glargine, lispro, aspart and human insulin). Longer-term studies are needed to further explore this issue.

## **AUTHOR CONTRIBUTION STATEMENT**

The work presented here was carried out with the involvement of every author. LG-B, DC, MM, AHB, FP-L, MP, BC, MRi, LM, J-FB, AK, MRo, JB, AA, and LA conceived both the research theme and the methods, analyzed the data and interpreted the results. LG-B was in charge of the study in France and in the United Kingdom, and together with AK, MRo and LA drafted and revised the paper. All authors have contributed to, read and approved the final manuscript. LG-B is guarantor for the study. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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**Guarantor for the study** Dr Lamiae Grimaldi-Bensouda is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Conflict of Interest statement** Lamiae Grimaldi-Bensouda (LG-B) was the recipient of a research fellowship from INSERM (French National Institute of Health and Medical Research) at the time of the study and is currently employed by LA-SER, the company conducting the study, together with Michel Rossignol (MRo) and Artak Khachatryan (AK). David Cameron (DC) received consulting fees and travel expenses during the design stage of ISICA from Sanofi-Aventis. Michel Marty (MM) has received consultancy fees from Sanofi-Aventis, Debiopharma, and Celgene; payment for development of educational presentations including service on speakers' bureaux from Roche and AstraZeneca; and reimbursement of

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